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## Description

This invention relates to improvements in the treatment of asthma and other respiratory disorders. More particularly, it relates to the use of a bronchodilator drug in combination with a steroidal anti-inflammatory drug for the treatment of respiratory disorders such as asthma, and to pharmaceutical compositions containing the two active ingredients.

Asthma is a condition characterised by variable, reversible obstruction of the airways which is caused by a complex inflammatory process within the lungs. In most cases, this process is initiated and maintained by the inhalation of antigens by sensitive atopic individuals (extrinsic asthma). However, in some patients it is caused by other mechanisms which at present are poorly understood but do not involve an allergic process (intrinsic asthma). The disease has therefore two components, spasm of the bronchial (or breathing) tubes and inflammation or swelling of the breathing tubes.

Salbutamol, the first highly selective  $\beta_2$ -adrenoceptor stimulant has been used successfully and effectively by inhalation for the immediate relief of spasm in asthma. However, when given by inhalation, salbutamol has usually a four to six hour duration of action, which is too short either to control nocturnal asthma or for convenient maintenance of the disease in some patients.

Anti-inflammatory corticosteroids such as, for example, beclomethasone dipropionate have also been administered by inhalation in the treatment of asthma, although unlike salbutamol the therapeutic benefits may not be immediately apparent. Indeed, although the benefits of inhaled beclomethasone dipropionate and its safety and efficacy in asthma therapy are well-established in clinical practice, the true nature of asthma as an inflammatory disease and the consequent fundamental effects of inhaled beclomethasone dipropionate in its treatment have only recently been realised.

It has, however, been recognised that asthma may be treated by using both a bronchodilator for immediate relief and a prophylactic anti-inflammatory corticosteroid to treat the underlying inflammation. Such combination therapy directed at the two main underlying events in the lung (i.e. relief of spasm in the breathing tubes and treatment of inflammation in the breathing tubes) using a combination of salbutamol and beclomethasone dipropionate has previously been proposed (Ventide, Glaxo Group trade mark), but suffers a number of disadvantages in view of the above-mentioned short duration of action exhibited by salbutamol. Thus the need for a 4-hourly dosing regimen may discourage effective patient compliance and also renders the product less than satisfactory in the treatment of nocturnal asthma since the bronchodilator may not remain effective for the duration of the night, leading to impaired sleep for asthmatics troubled by nocturnal cough, breathlessness and wheeze.

The present invention is based on the concept of a novel combination therapy which has greater efficiency and duration of bronchodilator action than previously known combinations and which permits the establishment of a twice daily (bis in diem - b.i.d) dosing regimen with consequent benefits in, for example, the treatment of asthma, particularly nocturnal asthma.

Thus we have found that if the  $\beta_2$ -adrenoreceptor stimulant bronchodilator salmeterol and/or a physiologically acceptable salt thereof is combined with beclomethasone dipropionate in a form suitable for administration by inhalation, the resulting compositions may be administered on a b.i.d. basis to provide effective treatment and/or prophylactic therapy for asthmatics. In particular such administration has been shown to lead to improvement in daytime lung function, requirement for additional symptomatic bronchodilator and almost complete abolition of nocturnal asthma while giving rise to minimal systemic side effects.

Salmeterol is one of a range of bronchodilators having extended duration of action which is described in GB-A- 2140800, and is systematically named 4-hydroxy- $\alpha^1$ -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol.

According to one aspect of the invention there are provided pharmaceutical compositions comprising effective amounts of salmeterol (and/or a physiologically acceptable salt thereof) and beclomethasone dipropionate as a combined preparation for simultaneous, administration by inhalation in the treatment of respiratory disorders.

The invention additionally relates to the use of salmeterol (and/or a physiologically acceptable salt thereof) and beclomethasone dipropionate in the manufacture of pharmaceutical compositions as combined preparations for simultaneous administration of salmeterol and beclomethasone dipropionate by inhalation in the treatment of respiratory disorders.

Suitable physiologically acceptable salts of salmeterol include acid addition salts derived from inorganic and organic acids, such as the hydrochloride, hydrobromide, sulphate, phosphate, maleate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate, methanesulphonate, ascorbate, salicylate, acetate, fumarate, succinate, lactate, glutarate, gluconate, tricarallylate, hydroxynaphthalenecarboxylate, e.g. 1-hydroxy- or 3-hydroxy-2-naphthalenecarboxylate or oleate. Salmeterol is

preferably used in the form of its 1-hydroxy-2-naphthalene carboxylate salt (hydroxynapthoate).

For administration by inhalation, the compositions according to the invention are conveniently delivered by conventional means i.e. in the form of a metered dose inhaler prepared in a conventional manner or in combination with a spacer device such as the Volumatic (Glaxo Group trade mark) device. In the case of a metered dose inhaler, a metering valve is provided to deliver a metered amount of the composition. Spray compositions may for example be formulated as aqueous solutions or suspensions and may be administered by a nebuliser. Aerosol spray formulations for example in which the active ingredients are suspended, optionally together with one or more stabilisers, in a propellant, e.g. a halogenated hydrocarbon such as trichlorofluoromethane, dichlorodifluoromethane, 1,2-dichlorotetrafluoroethane, trichlorotrifluoroethane, monochloropentafluoroethane, chloroform or methylene chloride may also be employed.

Alternatively, for administration by inhalation or insufflation, the compositions according to the invention may take the form of a dry powder composition, for example a powder mix of the active ingredients and a suitable carrier such as lactose. The powder compositions may be presented in unit dosage form in, for example, capsules, cartridges or blister packs from which the powder may be administered with the aid of an inhaler such as the Rotahaler inhaler (Glaxo Group trade mark) or in the case of blister packs by means of the Diskhaler inhaler (Glaxo Group trade mark).

The ratio of salmeterol to beclomethasone dipropionate in the compositions according to the invention is preferably within the range 2:1 to 1:40. Each metered dose or actuation of the inhaler will generally contain from 25 µg to 100 µg of salmeterol and from 50 µg to 1000 µg of beclomethasone dipropionate. As hereinbefore indicated, it is intended that the pharmaceutical compositions will be administered twice daily.

A suitable daily dose of salmeterol for inhalation is in the range 20 µg to 200 µg.

A suitable daily dose of beclomethasone dipropionate for inhalation is in the range of 100 µg to 2000 µg depending on the severity of the disease.

The precise dose employed will of course depend on the method of administration, the age, weight and condition of the patient and will be determined by the clinician depending on the severity and the type of asthma.

In order that the invention may be more fully understood, the following examples are given.

#### EXAMPLE 1 - Metered Dose Inhaler

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| <u>Active Ingredient</u>            | <u>Target per<br/>Actuation</u> | <u>Per Inhaler<br/>% w/w</u> |
|-------------------------------------|---------------------------------|------------------------------|
| Salmeterol<br>(as hydroxynapthoate) | 25.0 µg                         | 0.0448                       |
| Beclomethasone dipropionate<br>BP   | 50.0 µg                         | 0.0647                       |
| Stabiliser                          | 7.5 µg                          | 0.0110                       |
| Trichlorofluoromethane              | 23.67 mg                        | 27.8207                      |
| Dichlorodifluoromethane             | 61.25 mg                        | 72.0588                      |

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EXAMPLE 2 - Metered Dose Inhaler

| <u>Active Ingredient</u>            | <u>Target per Actuation</u> | <u>Per Inhaler % w/w</u> |
|-------------------------------------|-----------------------------|--------------------------|
| Salmeterol<br>(as hydroxynapthoate) | 25.0 µg                     | 0.0448                   |
| Beclomethasone dipropionate<br>BP   | 100.0 µg                    | 0.1294                   |
| Stabiliser                          | 10.5 µg                     | 0.0129                   |
| Trichlorofluoromethane              | 23.62 mg                    | 27.7541                  |
| Dichlorodifluoromethane             | 61.25 mg                    | 72.0588                  |

EXAMPLE 3 - Metered Dose Inhaler

| <u>Active Ingredient</u>            | <u>Target per Actuation</u> | <u>Per Inhaler % w/w</u> |
|-------------------------------------|-----------------------------|--------------------------|
| Salmeterol<br>(as hydroxynapthoate) | 25.0 µg                     | 0.0448                   |
| Beclomethasone dipropionate<br>BP   | 250.0 µg                    | 0.3235                   |
| Stabiliser                          | 25.0 µg                     | 0.0324                   |
| Trichlorofluoromethane              | 23.45 mg                    | 27.5405                  |
| Dichlorodifluoromethane             | 61.25 mg                    | 72.0588                  |

EXAMPLE 4 Metered Dose Inhaler

|    | <u>Active Ingredient</u>             | <u>Target per<br/>Actuation</u> | <u>Per Inhaler<br/>% w/w</u> |
|----|--------------------------------------|---------------------------------|------------------------------|
| 5  |                                      |                                 |                              |
| 10 | Salmeterol<br>(as hydroxynaphthoate) | 100.0 µg                        | 0.1791                       |
| 15 | Beclomethasone dipropionate<br>BP    | 125.0 µg                        | 0.3235                       |
|    | Stabiliser                           | 25.0 µg                         | 0.0324                       |
| 20 | Trichlorofluoromethane               | 23.43 mg                        | 27.4062                      |
|    | Dichlorodifluoromethane              | 61.25 mg                        | 72.0588                      |

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In Examples 1 to 4 micronised beclomethasone dipropionate (as the trichlorofluoromethane solvate) and micronised salmeterol (as the hydroxynaphthoate) are added in the proportions given above either dry or after predispersal in a small quantity of stabiliser (disodium dioctylsulphosuccinate, lecithin, oleic acid or sorbitan trioleate)/trichlorofluoromethane solution to a suspension vessel containing the main bulk of the trichlorofluoromethane solution. The resulting suspension is further dispersed by an appropriate mixing system using, for example, a high sheer blender, ultrasonics or a microfluidiser until an ultrafine dispersion is created. The suspension is then continuously recirculated to suitable filling equipment designed for cold fill or pressure filling of dichlorodifluoromethane. Alternatively, the suspension may be prepared in a suitable chilled solution of stabiliser, in trichlorofluoromethane/dichlorodifluoromethane.

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EXAMPLE 5 - Metered Dose Dry Powder Formulation

|    | <u>Active Ingredient</u>  | <u>µg/cartridge or blister</u> |
|----|---|--------------------------------|
| 40 |   |                                |
| 45 | Salmeterol<br>(as hydroxynaphthoate)                            | 36.3                           |
|    | Beclomethasone dipropionate BP<br>(anhydrous or as monohydrate) | 50.00                          |
| 50 | Lactose Ph.Eur.   | to 12.5 mg or<br>to 25.0mg     |

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|    | <u>Active Ingredient</u>  | <u>µg/cartridge or blister</u> |
|----|---|--------------------------------|
| 5  | Salmeterol<br>(as hydroxynaphthoate)                            | 36.25                          |
| 10 | Beclomethasone dipropionate BP<br>(anhydrous or as monohydrate) | 100.00                         |
| 15 | Lactose Ph.Eur.   | to 12.5 mg or<br>to 25.0 mg    |

20 **EXAMPLE 7 - Metered Dose Dry Powder Formulation**

|    | <u>Active Ingredient</u>                                     | <u>µg/cartridge or blister</u> |
|----|--|--------------------------------|
| 25 | Salmeterol<br>(as hydroxynaphthoate)                         | 72.5                           |
| 30 | Beclomethasone dipropionate<br>(anhydrous or as monohydrate) | 100.00                         |
| 35 | Lactose Ph.Cur.  | to 12.5 mg or<br>to 25.0 mg    |

EXAMPLE 8 - Metered Dose Dry Powder Formulation

|    |                                |                                |
|----|--------------------------------|--------------------------------|
| 5  | <u>Active Ingredient</u>       | <u>µg/cartridge or blister</u> |
|    | Salmetreol                     | 72.5                           |
|    | (as hydroxynaphthoate)         |                                |
| 10 |                                |                                |
|    | Beclomethasone dipropionate BP | 200.00                         |
|    | (anhydrous or as monohydrate)  |                                |
| 15 |                                |                                |
|    | Lactose Ph.Eur.                | to 12.5 mg or                  |
|    |                                | to 25.0 mg                     |

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EXAMPLE 9 - Metered Dose Dry Powder Formulation

|    |                                |                                |
|----|--------------------------------|--------------------------------|
| 25 | <u>Active Ingredient</u>       | <u>µg/cartridge or blister</u> |
|    | Salmeterol                     | 72.5                           |
|    | (as hydroxynaphthoate)         |                                |
| 30 |                                |                                |
|    | Beclomethasone dipropionate BP | 500.0                          |
|    | (anhydrous or as monohydrate)  |                                |
| 35 |                                |                                |
|    | Lactose Ph.Eur.                | to 12.5 mg or                  |
|    |                                | to 25.0 mg                     |

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EXAMPLE 10 - Metered Dose Dry Powder Formulation

| 5  | <u>Active Ingredient</u>       | <u>µg/cartridge or blister</u> |
|----|--------------------------------|--------------------------------|
|    | Salmeterol                     | 72.5                           |
| 10 | (as hydroxynaphthoate)         |                                |
|    | Beclomethasone dipropionate BP | 1000.0                         |
|    | (anhydrous or as monohydrate)  |                                |
| 15 | Lactose Ph. eur.               | to 12.5 mg or                  |
|    |                                | to 25.0 mg                     |

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EXAMPLE 11 - Metered Dose Dry Powder Formulation

| 25 | <u>Active Ingredient</u>      | <u>µg/cartridge or blister</u> |
|----|-------------------------------|--------------------------------|
|    | Salmeterol                    | 145.0                          |
| 30 | (as hydroxynaphthoate)        |                                |
|    | Beclomethasone dipropionate   | 250.0                          |
|    | (anhydrous or as monohydrate) |                                |
| 35 | Lactose Ph. Eur.              | to 12.5 mg or                  |
|    |                               | to 25.0 mg                     |

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In Examples 5 to 11 the active ingredients are micronised and bulk blended with the lactose in the proportions given above. The blend is filled into hard gelatin capsules or cartridges or in specifically constructed double foil blister packs (Rotadisks blister packs, Glaxo Group trade mark) to be administered by an inhaler such as the Rotahaler inhaler (Glaxo Group trade mark) or in the case of the blister packs with the Diskhaler

45 inhaler (Glaxo Group trade mark).

**Claims**

- 50
1. Products containing salmeterol (and/or a physiologically acceptable salt thereof) and beclomethasone dipropionate as a combined preparation for simultaneous administration by inhalation in the treatment of respiratory disorders.
  2. Products as claimed in claim 1 wherein salmeterol is present as its 1-hydroxy-2-naphthalenecarboxylate salt.
  3. Products as claimed in claim 1 or claim 2 presented in the form of a metered dose inhaler or a metered dry powder composition.
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4. Products as claimed in any of claims 1 to 3 in dosage unit form containing 25-100µg of salmeterol (optionally in the form of a physiologically acceptable salt thereof) and 50-1000µg of beclomethasone dipropionate per dosage unit.
- 5 5. The use of salmeterol (and/or a physiologically acceptable salt thereof) and beclomethasone dipropionate in the manufacture of pharmaceutical compositions as combined preparations for simultaneous administration of salmeterol and beclomethasone dipropionate by inhalation in the treatment of respiratory disorders.
- 10 6. The use of salmeterol (and/or a physiologically acceptable salt thereof) and beclomethasone dipropionate according to claim 5 in the manufacture of pharmaceutical compositions for administration on a twice daily basis.

#### 15 Patentansprüche

1. Produkte, enthaltend Salmeterol (und/oder ein physiologisch verträgliches Salz davon) und Beclomethasondipropionat als Kombinationspräparat zur gleichzeitigen Verabreichung durch Inhalation bei der Behandlung von Atemstörungen.
- 20 2. Produkte nach Anspruch 1, wobei Salmeterol als sein 1-Hydroxy-2-naphthalincarbonsäuresalz vorliegt.
3. Produkte nach Anspruch 1 oder 2, in Form eines Dosierinhalators oder einer abgemessenen Trockenpulverzusammensetzung.
- 25 4. Produkte nach einem der Ansprüche 1 bis 3 in Einheitsdosisform, enthaltend 25-100 µg Salmeterol (gegebenenfalls in Form eines physiologisch verträglichen Salzes davon) und 50-1000 µg Beclomethasondipropionat pro Dosiereinheit.
- 30 5. Verwendung von Salmeterol (und/oder einem physiologisch verträglichen Salz davon) und Beclomethasondipropionat bei der Herstellung von Arzneimitteln als Kombinationspräparate zur gleichzeitigen Verabreichung von Salmeterol und Beclomethasondipropionat durch Inhalation bei der Behandlung von Atemstörungen.
- 35 6. Verwendung von Salmeterol (und/oder einem physiologisch verträglichen Salz davon) und Beclomethasondipropionat gemäß Anspruch 5 bei der Herstellung von Arzneimitteln zur Verabreichung auf der Basis einer zweimal täglichen Gabe.

#### Revendications

- 40 1. Produits contenant du salmétérol (et/ou un sel physiologiquement acceptable de celui-ci) et du dipropionate de béclométhasone, sous forme de préparation combinée destinée à l'administration simultanée par inhalation pour le traitement de troubles respiratoires.
- 45 2. Produits suivant la revendication 1, caractérisés en ce que le salmétérol est présent sous forme de son 1-hydroxy-2-naphtalénecarboxylate sel.
3. Produits suivant la revendication 1 ou 2, présentés sous la forme d'un inhalateur à dose mesurée ou d'une composition en poudre sèche dosée.
- 50 4. Produits suivant l'une quelconque des revendications 1 à 3, sous forme de dose unitaire contenant de 25 à 100 µg de salmétérol (éventuellement sous forme d'un sel physiologiquement acceptable de celui-ci) et 50 à 1000 µg de dipropionate de béclométhasone par dose unitaire.
- 55 5. Utilisation de salmétérol (et/ou d'un sel physiologiquement acceptable de celui-ci) et du dipropionate de béclométhasone pour la fabrication de compositions pharmaceutiques sous forme de préparations combinées destinées à l'administration simultanée du salmétérol et du dipropionate de béclométhasone par inhalation en vue du traitement de troubles respiratoires.

6. Utilisation du salmétérol (et/ou d'un sel physiologiquement acceptable de celui-ci) et du dipropionate de bécloéthasone suivant la revendication 5 en vue de la fabrication de compositions pharmaceutiques destinées à l'administration sur une base biquotidienne.

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